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Reference Values for Aerobic Fitness in Children, Adolescents, and Young Adults Who Have Cerebral Palsy and Are Ambulatory

Olaf Verschuren, Manon Bloemen, Cas Kruitwagen, Tim Takken

Background. Very few objective data regarding aerobic performance in young people with cerebral palsy (CP) exist. The characterization of aerobic fitness could provide baseline and outcome measures for the rehabilitation of young people with CP.

Objective. The objective of this study was to provide reference values for aerobic fitness in a group of children, adolescents, and young adults who had CP and who were classified at Gross Motor Function Classification System (GMFCS) level I or II. Data were collected with 10-m shuttle run tests.

Design. This investigation was a cross-sectional observational study conducted between August 2008 and June 2009.

Methods. Data from a total of 306 children, adolescents, and young adults who had CP, who were 6 to 20 years old, and who were recruited from 26 rehabilitation centers in the Netherlands, Switzerland, Australia, Canada, and the United States were used for establishing reference values. A total of 211 participants were classified at GMFCS level I (mean age=12.2 years, SD=3.0), and 95 were classified at GMFCS level II (mean age=12.4 years, SD=3.2); 181 were male, and 125 were female. Aerobic fitness was reflected by the level achieved on the 10-m shuttle run tests.

Results. On the basis of a total of 306 assessments from the 10-m shuttle run tests, 4 reference curves were created.

Limitations.

Conclusions. This study provided height-related reference values for aerobic fitness in children, adolescents, and young adults who had CP, who were 6 to 20 years old, and who were classified at GMFCS level I or II. Generalized additive models for location, scale, and shape were used to construct centile curves. These curves are clinically relevant and provide a user-friendly method for the prediction of aerobic fitness in young people with CP.

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Aerobic fitness may be defined as the ability to deliver oxygen to the muscles and to utilize it to generate energy during exercise; it often is presented as peak oxygen uptake (VO_2peak).[1] Peak oxygen uptake is strongly associated with health and disease in adulthood.[2,3] Moreover, it is a strong indicator of functional capacity and mortality in adulthood.[4] Maintaining an appropriate level of aerobic fitness reduces the risk of disease and injury and increases the abilities to work efficiently and to participate in and enjoy physical activity (sports, recreation, and leisure).[5,6] A high aerobic fitness level has an impact on optimum health and prevents the onset of problems associated with inactivity at all ages.[2,5–7] Research consistently has shown that people with cerebral palsy (CP) have low VO_2peak values.[8,9] These low levels of VO_2peak affect both daily and recreational activities and could have significant implications for health in people with CP.[10]

An appropriate method for assessing aerobic fitness is a test of progressive exercise to exhaustion, in which the highest exercise intensity achieved (eg, peak work load, endurance time) is a parameter of aerobic fitness.[11,12] The gold standard for determining aerobic fitness is a direct measurement of VO_2peak during such a test.[13] However, a direct measurement of VO_2peak usually is not feasible because it requires specialized respiratory gas analysis equipment, which typically is not available in clinical, rehabilitation, or field settings and often is not tolerated by younger children with CP.

Shuttle run tests are useful measures of aerobic fitness. These field tests, in which participants walk or run between 2 markers, can easily be administered in a clinical setting. For young people who have CP and who are able to walk independently, 2 reliable and valid 10-m shuttle run test protocols are available: shuttle run test I (SRT-I) and shuttle run test II (SRT-II) for young people classified at Gross Motor Function Classification System (GMFCS)[14,15] levels I and II, respectively. Both shuttle run tests have several characteristics that are similar to those of the accepted gold standard.[16]

Aerobic fitness measured with shuttle run tests reflects the overall capacity of the cardiovascular, respiratory, and muscular systems and the ability to carry out prolonged strenuous exercise.[17] The progression of aerobic fitness has been well established in people who are healthy and have no disabilities from childhood through adolescence.[18] Aerobic fitness increases with age and is at its peak in childhood and late adolescence.[18] The literature fails to provide objective data regarding aerobic fitness in young people with CP. The characterization of aerobic fitness could provide baseline and outcome measures for the rehabilitation of young people with CP.

Therefore, the aim of this study was to provide reference data for aerobic fitness in 306 children, adolescents, and young adults who had CP, who were from various geographic regions, and who were classified at GMFCS level I or II. Data were collected with the SRT-I and the SRT-II.

Method

Procedure and Participants

The SRT-I and the SRT-II were implemented in 17 rehabilitation centers and schools for special education in the Netherlands between August 2008 and June 2009. The tests also were implemented in rehabilitation centers in Switzerland (n=3), Australia (n=3), Canada (n=2), and the United States (n=1). During the implementation process, the pediatric physical therapists and exercise physiologists were trained both theoretically and practically in executing the shuttle run tests. All therapists or exercise physiologists at the participating centers performed the shuttle run tests under the supervision of the developers of the tests and were instructed to follow the guidelines described in the Appendix throughout the data collection period. Trained therapists or exercise physiologists were asked to return the data obtained from testing of young people with CP in their clinics by using a standardized Microsoft Word or Excel data sheet.*

Data included in this study were from children, adolescents, and young adults who were 6 to 20 years old, were diagnosed with spastic CP, and were classified at GMFCS level I or II. All participants were receiving physical therapy or were assessed during an examination at a clinic follow-up visit. Cognitively, they had to be able to follow simple commands. Young people were excluded if they had had orthopedic surgery or neurosurgery within 6 months before study entry or cardiac or respiratory conditions that could be adversely affected by exercise. Young people who were considered to be athletes with CP (more than 10 hours of formal exercise training per week) also were excluded. Besides data on test performance, information regarding the assessment dates, diagnosis, GMFCS level, date of birth, height, weight, and sex was collected.

Measurements

Anthropometry. Participants' body mass and height were measured in a standardized manner. Before testing, each child was weighed in underwear to the nearest 100 g on the digital scales available in the participating clinics. Height measurements were taken on the same day while each child was standing against a

* Microsoft BV, Amsterdam, the Netherlands.

AQ: 26

Table.
Participant Characteristics[a]

Participants	Variable	GMFCS Level I[b]				GMFCS Level II[c]			
		$\bar{X}$	SD	Median	Range	$\bar{X}$	SD	Median	Range
Male	Age (y)	12.1	2.7	11.6	6–19	12.6	3.5	12.5	7–19
	Height (cm)	151.1	15.8	151.0	118–187	150.7	19.9	149.3	122–190
	Body mass (kg)	44.0	14.5	41.0	20–92	43.4	15.8	41.0	23–88
	BMI (kg/m^2)	18.7	3.6	18.1	12.7–29.7	18.5	3.3	18.1	14.2–26.5
Female	Age (y)	12.3	3.2	12.3	7–19	12.2	2.7	12.6	6–17
	Height (cm)	149.2	17.8	150.0	117–181	140.8	14	142	115–178
	Body mass (kg)	45.6	17.2	44.0	19–85	38.3	13.0	34.0	20–90
	BMI (kg/m^2)	19.7	4.0	19.2	13–30.5	19.0	4.2	17.6	13.0–30.5

[a] GMFCS=Gross Motor Function Classification System, BMI=body mass index.
[b] n=133 male participants and 78 female participants.
[c] n=48 male participants and 47 female participants.

wall. Height was measured to the nearest 0.5 cm with a stadiometer or wall-mounted measuring stick. The body mass index was calculated as weight in kilograms divided by height in meters squared.

GMFCS. The GMFCS was used by a pediatric physical therapist who was experienced with this classification system to classify the young people with CP on the basis of their functional mobility. Because of the characteristics of the shuttle run tests, only children, adolescents, and young adults who were classified at GMFCS level I (able to walk indoors and outdoors and climb stairs without limitations) or level II (able to walk indoors and outdoors and climb stairs holding onto a railing but experience limitations in walking on uneven or inclined surfaces and in walking in crowds or confined spaces) were included. The original GMFCS has been reported to yield reliable and valid data for children who are 6 to 12 years old.[14] Participants who were more than 12 years old were classified with the expanded and revised version of the GMFCS.[19] The physical characteristics of the participants (according to GMFCS level) are summarized in the Table. T1

Aerobic fitness. Aerobic fitness was reflected by the level achieved on the 10-m shuttle run tests.[16] In these tests, participants walk or run between 2 markers delineating the respective course of 10 m at a set incremental speed determined by a signal (every minute). The starting speeds for the tests are 5 and 2 km/h for participants who are classified at GMFCS levels I and II, respectively, and the speeds are increased by 0.25 km/h every minute. The last completed level (accurate to a half shuttle) was recorded and used for analysis. These tests have been shown to be reliable, valid, and sensitive to change in children with CP.[16,20]

Each participant's heart rate was measured continuously with a portable heart rate monitor. All participants were instructed to walk or run until exhaustion. One objective criterion and 2 subjective criteria were used to determine whether the tests were maximal. Each child had to meet the objective criterion and 1 of the 2 subjective criteria at the end of the tests. The physiological objective criterion was a heart rate of greater than or equal to 180 bpm.[21] The subjective criteria were signs of intense effort, such as an unsteady walking or running pattern, sweating, facial flushing, and a clear unwillingness to continue walking or running despite repeated strong verbal encouragement. Further details on the preparation of the participants and procedures were published previously.[16]

Data Analysis

Cross-sectional data analyses were performed with SPSS version 15.0[†] and the R statistical program.[‡] Data for male and female participants are presented separately. Fn† Fn‡

Data from all participants, GMFCS levels I and II and male and female participants together, were analyzed with generalized additive models for location, scale, and shape (GAMLSS).[23] This method is similar to those used for the growth standard recently published by the World Health Organization.[24] The GAMLSS method extends the LMS method[25] in several ways.[26] Generalized additive models for location, scale, and shape are parametric or semiparametric regression-type models in which various distribution functions can be compared to find AQ: 9 AQ: 10 AQ: 11

[†] SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.
[‡] R Foundation for Statistical Computing, Vienna, Austria.

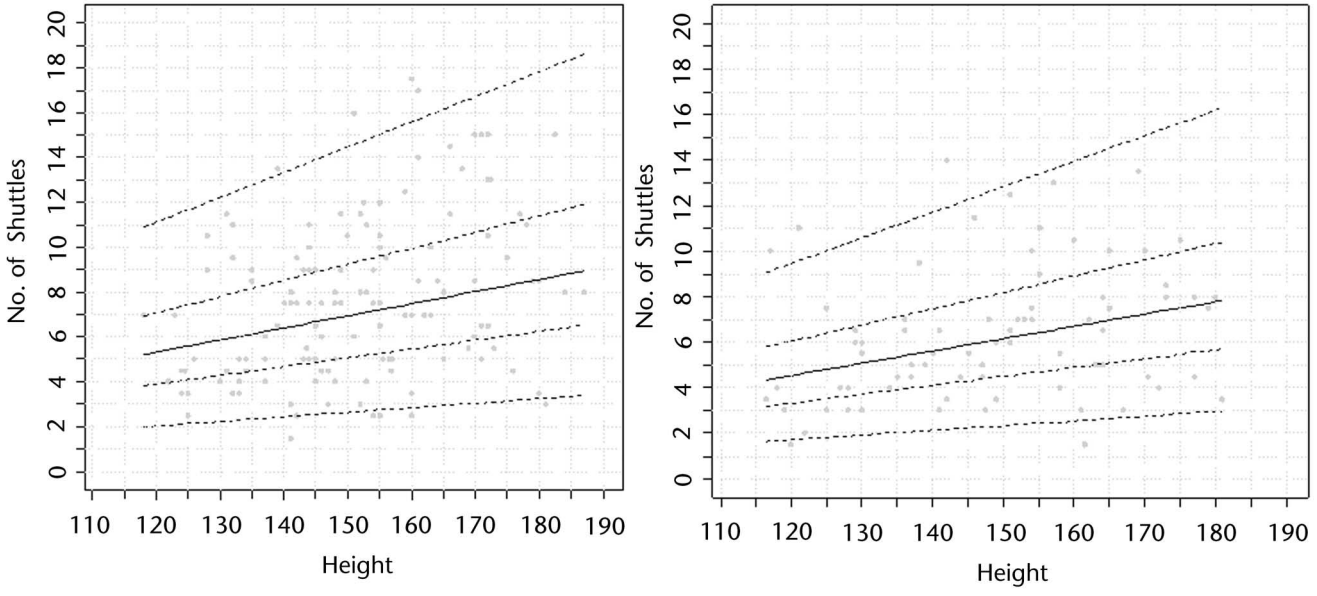

Figure 1.
Reference centile curves for 10-m shuttle run test I for male participants (left) and female participants (right) classified at Gross Motor Function Classification System level I. The test started at 5 km/h. Height was measured in centimeters.

the best distribution for the data.[26] They offer a choice of error distributions (rather than just one), can process general linear predictors for each moment parameter (rather than being limited to a single covariate), and offer a choice of links between predictors and outcomes AQ: 12

In preliminary analyses, height showed the best correlation with shuttle run test performance. As possible predictors, therefore, we included GMFCS level, sex, height, and their interactions. Next, model building was performed for each test (dependent variable) to determine the significant predictor variables and their effect sizes, and formulas were constructed from these models. All data were used for model building. The larger number of participant classified at GMFCS level I increased the stability for the curves created for GMFCS level II. Separate graphs of the resulting models were made according to GMFCS level and sex.

Role of the Funding Source
This research was supported by the Dr W.M. Phelps Foundation, Bussum, the Netherlands. The funding body did not participate in the design or execution of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the article.

Results
Data from 306 participants in the Netherlands (n=170), Switzerland (n=41), Australia (n=68), Canada (n=13), and the United States (n=14) were used for establishing reference values. A total of 211 participants were classified at GMFCS level I, and 95 were classified at GMFCS level II; 181 were male, and 125 were female. The physical characteristics of the male and female participants classified at GMFCS level I (Table) were not significantly different. The physical characteristics of the male and female participants classified at GMFCS level II (Table) were comparable, except for height; the male participants were significantly taller than the female participants.

The mean heart rate of the participants at peak exercise was 194±10 bpm, indicating good effort during exercise. No injuries, complaints of pain, or other medical problems occurred in the participants completing the shuttle run tests. Figures 1 and 2 show the height-related centile curves (P3, P25, P50, P75, and P97) for both sexes and GMFCS levels; these centile curves were calculated by use of a gamma distribution. AQ: 13 AQ: 14 F1 F2

Discussion
This study provided an objective characterization of aerobic fitness in relation to the height of children, adolescents, and young adults who had CP and who were from various geographic regions. Generalized additive models for location, scale, and shape were used to construct centile curves. These curves are clinically relevant and provide a user-friendly method for the prediction of aerobic fitness.

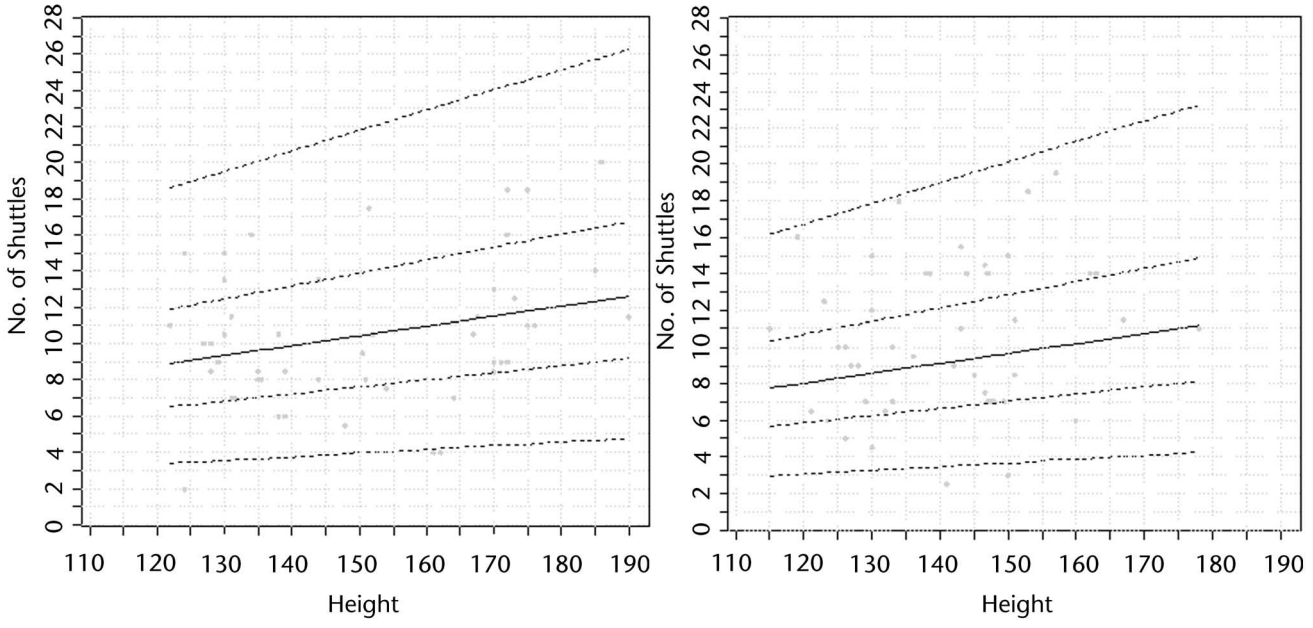

Figure 2.
Reference centile curves for 10-m shuttle run test II for male participants (left) and female participants (right) classified at Gross Motor Function Classification System level II. The test started at 2 km/h. Height was measured in centimeters.

The results of this study showed that with increasing height, children, adolescents, and young adults achieved a larger number of shuttles on the SRT-I and the SRT-II. These findings are comparable to those for their peers who are developing typically, in whom performance on shuttle run tests increases with age and height.[27] Aerobic performance values have been shown to be consistently higher in boys who are developing typically than in girls, and the sex difference becomes more pronounced as children progress through adolescence.[27] The results of the present study showed that male and female participants with CP had increases in their shuttle run performance during development that were similar to those of their peers who are developing typically. Male participants were found to accomplish more shuttles than female participants. These results may have been attributable to their greater muscle mass and cardiac output and the ability to achieve higher levels of physical activity during development.[13] Because these differences between the sexes were consistent across the countries, they were probably biological rather than social in origin.

Both shuttle run tests typically involve speed being increased systematically as a function of time until the participants are unable to continue. Theoretically, at the limit of tolerance, well-motivated participants will have achieved their maximal (exercise mode–specific) heart rates. A continuous progressive exercise test should ideally result in exhaustion between 6 and 12 minutes.[28] For the SRT-I, the median exercise time was 7 (±3.4) minutes, and for the SRT-II, the median was 10 (±4.0) minutes. These data indicate that both shuttle run tests are suitable, efficient, and within current recommendations. Moreover, both tests also have been shown to be sensitive to change in children with CP.[20]

In clinical practice, the safety of running–based maximal exercise testing for children with CP is a concern. As a result, less intense exercise testing, such as the Six-Minute Walk Test, has been used routinely for children with CP. Despite evidence supporting the usefulness of the Six-Minute Walk Test, the information gathered from the test remains limited because the only measurements obtained are related to distance walked.[29,30] In contrast, maximal exercise testing, like 10-m shuttle run testing, provides more information related to aerobic fitness.[17] Four studies that described data regarding maximal aerobic fitness in children and adolescents with CP reported no adverse effects.[9,16,31,32] These data indicate that maximal exercise testing for children and adolescents with CP is suitable and safe.

AQ: 15

AQ: 16

Height was used instead of age for the construction of the standard reference curves because, among all of the anthropometric factors that were proven to have a significant correlation with the shuttle run tests, height was the most discriminative variable;

AQ: 17

it showed the highest correlation with shuttle run test performance. Height is an anthropometric parameter that is routinely recorded in all medical records in pediatric clinics. In addition, height is a more robust parameter than age, because people of the same age but with different backgrounds can have substantial differences in height.[33] In the present study, no information regarding ethnicity was gathered. Reference values for aspects of fitness in children who are developing typically vary in different countries.[34] The use of height-specific curves might lessen such variations, but further studies including the ethnicity of the participants in the analyses are needed for a formal comparison.[35]

The limitation of the present study is the cross-sectional nature of the design. Given the difficulty of recruiting special populations to start with, it would be quite difficult to conduct a similar study with a longitudinal design. Certainly, this is an area for future research; future longitudinal research with a smaller cohort should confirm the height-related increase in performance reported here

The shuttle run test that often is used for children who are developing typically is the 20-m shuttle run test described by Leger et al.[36] For most children with CP, this test is not suitable, because the starting speed (8 km/h) and the increase (0.5 km/h) every minute are beyond their capabilities. Only 2 of the 68 participants who had CP (classified at GMFCS level I or II) and who participated in an exercise training program had a peak running speed of greater than 8 km/h on the SRT-I or the SRT-II at baseline.[20,37] Because the running speed of children with CP is different from that of children who are developing typically, it is not possible to compare the performance of both groups of children on the same shuttle run test.

Although all therapists from the participating centers were instructed to follow the guidelines described in the Appendix, we are not aware of the interrater and intrarater reliability across sites and testers. This limitation of the present study needs to be investigated in future research.

Moreover, the data used in the present study were from an "open-source" convenience sample of children, adolescents, and young adults who had CP and who were receiving physical therapy or were assessed during an examination. Most of the physical therapy took place in rehabilitation centers or schools for special education because most of the therapists who received the training for conducting the tests were working either in a rehabilitation center or in a school for special education. This situation may have led to selection bias, as data from young people who were not receiving treatment in a rehabilitation center or school for special education may have been missed. In addition, children, adolescents, and young adults who have CP and who do not attend a school for special education or a rehabilitation facility may be the young people with the highest exercise performance. This situation affects the generalizability of the reference values reported here to the clinical CP population. For future research, measuring physical activity with a physical activity questionnaire or an objective measure such as an activity monitor would provide important baseline information that would be useful for interpreting exercise testing results.

Caution also should be taken when our centile curves are applied to people who fall outside the characteristics of our cohort, such as those younger than 6 years and older than 19 years. The performance of people older than 19 years on shuttle run tests has not been investigated yet.

In conclusion, we used state-of-the-art statistical modeling techniques to provide reference values for aerobic fitness in relation to height for children, adolescents, and young adults who have CP, who are 6 to 20 years old, and who are classified at GMFCS levels I and II. The centile curves are clinically relevant and provide a user-friendly method for the prediction of aerobic fitness in young people with CP.

Dr Verschuren, M• Bloemen, and Dr Takken provided concept/idea/research design. All authors provided writing, data analysis, and consultation (including review of manuscript before submission). Dr Verschuren and M• Bloemen provided data collection. Dr Verschuren provided project management and fund procurement. The authors thank all of the therapists who participated in the data collection.

This study was approved by the local ethics committees of the participating rehabilitation centers.

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Appendix.

Guidelines for 10-m Shuttle Run Tests

Measurement: aerobic capacity

Population: children, adolescents, and young adults who had cerebral palsy and who were classified at Gross Motor Function Classification System (GMFCS) levels I and II

Equipment required: flat, nonslip surface; marking cones; measuring tape; 2 shuttle run test CDs; CD player; recording sheets; heart rate monitor

Preparations and conditions

The course is 10 m long. Mark each end of the course with the marking cones and measuring tape. Participants should wear sports clothing and shoes (and orthoses, if applicable). Each participant also should wear a heart rate monitor.

Shuttle Run Test protocol

Participants walk or run between 2 markers at a set incremental speed.

GMFCS protocols

There are 2 CDs for the shuttle run tests. Shuttle run test I (SRT-I) is for children, adolescents, and young adults classified at GMFCS level I. The SRT-I starts at a speed of 5 km/h. Shuttle run test II (SRT-II) is for children, adolescents, and young adults classified at GMFCS level II. The SRT-II starts at 2 km/h. Speed is increased by 0.25 km/h every minute in each test. Each CD begins with a brief introduction to the test. The introduction is followed by a 5-second countdown to the start of the test. Thereafter, the CD emits a single beep at regular intervals.

AQ: 24

- The walking or running pace is determined by a series of beeps on the accompanying CD.
- The participant should walk or run to the opposite end of the course when the first beep sounds. The participant should then continue walking or running at this speed, aiming at the opposite end of the course each time there is a beep.
- The participant should always place 1 foot either on or behind the 10-m mark at the end of each shuttle. If the participant arrives at the end of the shuttle before the beep sounds, then he or she should turn around, wait for the beep, and resume an adjusted walking or running speed.
- The walking or running speeds at the start of the test are very slow. On the SRT-I and the SRT-II, the participant has 7.2 and 18 seconds, respectively, to walk or run the 10-m shuttle.
- The walking or running speed is gradually increased. After each minute, the time interval between beeps decreases. The first speed is referred to as "level 1," the second speed is referred to as "level 2," and so on.
- Each level lasts approximately 1 minute, and each CD continues up to level 23. The end of each shuttle is denoted by a single beep; the end of each half level is denoted by a double beep; and the end of each level is denoted by a double beep and by the commentator on the CD.
- The test is finished when the participant is more than approximately 1.5 m (no markers necessary) away from the marker 2 consecutive paced signals within 1 level.
- The participant is instructed to walk or run for as long as possible, until he or she can no longer keep up with the speed set by the CD, at which point he or she should voluntarily withdraw from the test. In some cases, the person conducting the test may need to withdraw the participant when it becomes apparent that he or she is dropping behind the required pace and is unable to reach the marker on 2 consecutive shuttles.
- The test result is measured in units of a "level" (eg, 13) and a "half level" (eg, 14.5). The final level that a participant has completed is recorded on a recording sheet.
- The heart rate is read from the wrist monitor at the end of the test and recorded on a recording sheet. This heart rate can be used to determine whether a participant has performed maximally (a heart rate of >180 bpm).

Some participants find it difficult to coordinate their walking or running speed with the pace of the audio signal. Therefore, it is recommended that someone assist participants during the first stages of the test. Once participants understand the instructions, they can continue the test without assistance. Participants who continue to experience difficulty pacing themselves should be accompanied throughout the test. In this situation, an additional person is required to accompany a participant to ensure the reliability and validity of the test.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES 1

1—AQ1: According to the **AMA Manual of Style, referents for age groups are as follows: for ages 1 through 12, "children," "boys," or "girls"; for ages 13 through 17, "adolescents," "adolescent boys," or "adolescent girls"; for ages 18 and older, "adults" (for ages 18 through 24, "young adults" is also acceptable). Therefore, the referents in this article have been changed accordingly. When these specific changes would have been too cumbersome, "young people," "male participant," "female participant," "male and female participants," or "participant" was used. Please check all changes carefully throughout.**

2—AQ2: Please specify each author's job title at each affiliation listed. Also, is it correct to add "Utrecht" as the city for the Network for Childhood Disability Research? If not, please supply the correct city. In addition, elements of affiliations should be arranged in order from smallest to largest (eg, department, institution, city, country); elements in some affiliations were transposed in accordance with this guideline. Please check all affiliations carefully for accuracy.

3—AQ3: Please note that the terms "objective" and "subjective," as defined in APTA's Standards for Tests and Measurements, refer specifically to reliability. Can the terms "objective" and "subjective" be changed to other terms—eg, "quantitative" and "qualitative" or something similar—throughout the article?

4—AQ4: Please supply a short sentence on the limitations of this study, if applicable ("Limitations" is one of the section headings used in abstracts of observational studies).

5—AQ5: The first sentence in the "Conclusions" paragraph of the abstract was long and complex, so it was divided into 2 sentences. Please ensure that your intended meaning has been preserved.

6—AQ6: subscript format of "peak" was removed throughout for consistency with how VO_2 **designations are presented in the AMA Manual of Style.**

7—AQ7: OK to replace the term "gender" with the term "sex" throughout? **PTJ generally prefers to use the term "sex," which refers to the biological characteristics of males and females. The term "gender" includes more than sex and serves as a cultural indicator of a someone's personal and social status.**

8—AQ8: Study approval statement was moved to end of article per PTJ style. Did the participants or their parents provide signed informed consent?

9—AQ9: "accurate to a half shuttle" correct for "half shuttles accurate"? If not, please explain what is meant.

10—AQ10: Change of "were instructed to run" to "were instructed to walk or run" OK? Please check throughout (eg, "walking or running" later in paragraph).

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

11—AQ11: Please spell out "LMS."

12—AQ12: Sense of sentence beginning "They offer" OK as edited?

13—AQ13: Is it correct to add "Bussum" as the city for the Dr W.M. Phelps Foundation? If not, please supply the correct city. Also see end of article, where this information is repeated.

14—AQ14: Is "±10" a standard deviation or a standard error?

15—AQ15: OK to change "between 6 to 10–12" to "between 6 and 12"? If not, please explain why.

16—AQ16: Are the ± values in parentheses standard deviations or standard errors?

17—AQ17: Current recommendations for what and by whom? Any reference available for "current recommendations"?

18—AQ18: Sense of sentence beginning "Height was used" OK as edited? If not, please clarify meaning.

19—AQ19: OK to change "current height related increase in performance" to "height-related increase in performance reported here"? If not, please clarify what is meant.

20—AQ20: OK to change "Mostly, this was performed during physical therapy" to "Most of the physical therapy took place"?

21—AQ21: "young adults" was changed to "people older than 19 years" because "young adults" has been used throughout to describe some members of your cohort (see earlier note about referents for age groups).

22—AQ22: Your list of the authors' contributions to this study has been reworded in accordance with PTJ's preferred wording. Please make sure that your wording has been correctly interpreted. If any authors provided participants, facilities/equipment, institutional liaisons, or clerical/secretarial support, please so indicate. Also, please correct any incorrect salutations and provide a salutation (eg, Mr, Ms) for Manon Bloemen.

23—AQ23: Unable to find reference 23 at National Library of Medicine or Library of Congress. Please provide name of journal, date of publication, and volume and page numbers or, if this is a book, provide name and address of publisher and date of publication. If this is from a Web site, please provide the URL and the date on which you accessed it.

24—AQ24: Callout for Figure 1 was deleted here because the figure does not appear to show this information.

25—AQ25: Please give complete mailing addresses for Microsoft BV and R Foundation for Statistical Computing.

26—AQ26: The Table and the legends for Figures 1 and 2 were not included in your final revised

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES **3**

manuscript. These items were taken from the version preceding the final revision. Is this OK? If not, please supply these items.